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Favorable reconsideration of the application is respectfully requested in view of the foregoing amendment and the following remarks.

Claims 1, 2, 4, 7, 8, 13, 14 and 16 are pending in the application. Claims 1, 2, 4, 7, 8, 13, 14 and 16 have been rejected. Claims 1, 8 and 13 have been amended. Claims 2, 4, 14 and 16 have been cancelled without prejudice. No new matter has been added.

Claims 2 and 14 have been objected to under 37 CFR §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. As claims 2 and 14 have been cancelled without prejudice, this objection is rendered moot.

Claims 1, 2, 4, 7, 13, 14 and 16 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner states *inter alia* "it is not clear what is meant by the recitation that R11 is a hydrocarbon group comprising one single linear chain having a length of from 5 to 6 carbon atoms as the longest chain on carbon atom no. 11 of the steroid skeleton, as recited for example in claims 1 and 13."

In response, claims 1 and 13 have been amended to recite that R11 is selected from specific side-chain groups and claims 2, 4, 14 and 16 have been cancelled without prejudice.

In view of the above, withdrawal of the rejection of claims 1, 7 and 13 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 1, 2, 4, 7, 8, 13, 14 and 16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lobaccaro et al., J. Med. Chem, Vol 40, pp. 2217-2227, 1997 (Lobaccaro et al.). The Examiner essentially contends that since 1) Lobaccaro et al. refers to the compound 5b as being "estrogenic"; 2) the presently claimed compounds are homologs of the 11 β -n-alkyl estradiol derivatives described in Lobaccaro et al. and thus are expected to have similar properties to the compounds as taught by Lobaccaro et al., such as estrogenic activity; and 3) the length of the 11 β -n-alkyl arm affects the binding affinity for the estrogen receptor; it would have been obvious to a person of ordinary skill in the art at the time the invention was made to provide C5 or C6 homologs of the Lobaccaro et al. C4 compound with the expectation of providing a compound with similar properties.

As claims 2, 4, 14 and 16 have been cancelled without prejudice, and independent claims 1, 8 and 13 have been amended, Applicants address the §103 rejection with respect to the amended claims. Applicants traverse the rejection and respectfully submit that Lobaccaro et al. do not make obvious amended independent claims 1, 8 and 13.

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Lobaccaro et al. is directed to the development of steroidal affinity labels of the estrogen receptor, in particular, two estradiol 11 β -ethyl derivatives, three estradiol 11 β -butyl derivatives, and one estradiol 11 β -decyl derivative. Lobaccaro does not teach or specifically suggest the 11 β -n-alkyl estradiols having the specific R11 groups (having a total of 5-6 carbon atoms) as set forth in amended independent claims 1, 8 and 13.

With respect to the Examiner's statement that Lobaccaro et al. refer to the compound 5b as being "estrogenic", it is noted that compound 5b of Lobaccaro et al. was just used as a reference compound, next to estradiol. Compound 5b is not a steroidal affinity label of the estrogen receptor in accordance with Lobaccaro et al., since it does not contain an 11 β -terminal electrophilic functionality (see the first sentence of the Abstract and page 2220, left column, last paragraph). Accordingly, compound 5b was not a compound that the research of Lobaccaro et al. was primarily focused on.

With respect to the Examiner's statement that "it is considered that the instantly claimed compounds are homologous to the compound of Lobaccaro et al. and thus are expected to have similar properties to the compound as taught by Lobaccaro et al. such as estrogenic activity", it is asserted that the compounds recited in amended claim 1 having the recited R11 groups do not possess similar properties to the compound taught by Lobaccaro et al. In this regard, the Examiner's attention is directed to Compound 5b of Lobaccaro et al. which is compound 2 in Table B of the present application. As can be seen from the results in Table A, compound 2 possesses ER α agonist/ER β agonist activity, which is in contrast to the structurally-closest compound of one more carbon atoms, i.e., compound 3 (recited in amended claim 1) which possesses ER α agonist/ER β antagonist activity. Accordingly, compound 3 of the present invention does not possess similar properties to the compound 2 homolog described in Lobaccaro et al.

With respect to the Examiner's statement that Lobaccaro et al. teach that the length of the 11 β -n-alkyl arm affects the binding affinity for the estrogen receptor, Lobaccaro et al. fail to teach or specifically suggest that homologs such as compound 3 of the present invention would possess both ER- β antagonist and ER- α agonist activity. In this regard, the Examiner's attention is directed to page 2221, column 1 which refers to Table 2. Therein, it states:

"Activity of the electrophilic compounds (Figure 3, Table 2) was not correlated with the whole 11 β -substituent, but rather with the alkyl part of the substituent, since the two estradiol 11 β -ethyl derivatives 12a and 13a mainly displayed estrogenic activity, wherein the three estradiol 11 β -butyl derivatives 12b, 13b, and 14 and the 11 β -decyl derivative 20 showed almost pure antiestrogenic activity."

The Examiner's attention is also directed to page 2223, column 1, second paragraph, which states:

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"The estradiol electrophilic 11 β -derivatives proved to be either [emphasis added] estrogenic (11 β -ethyl compounds) or antiestrogenic (11 β -butyl and 11 β -decyl compounds)."

Accordingly, Lobaccaro et al. does not teach or specifically suggest that the described 11 β -n-alkyl estradiol derivatives have both agonist and antagonist activity, but instead that the 11 β -n-alkyl estradiol derivatives with an alkyl arm of 2 carbon atoms possess agonist activity whereas the 11 β -n-alkyl estradiol derivatives with an alkyl arm of 4 or 10 carbon atoms possess antagonist activity. Indeed, Lobaccaro only studies agonism and antagonism of "the estrogen receptor", and does not distinguish between the ER α and the ER β receptor, i.e., the focus of the present invention. In view that 1) Lobaccaro et al.'s interest was in studying the estrogen receptor using estradiol derivatives with a terminal electrophilic group, and 2) Lobaccaro et al. is completely silent about distinguishing between the ER α and the ER β receptor, one skilled in the art would not be motivated to rely on Lobaccaro et al. to solve the problem of finding a compound that possessed both ER α agonist and ER β antagonist activities.

Since Lobaccaro et al. does not provide the motivation to arrive at a compound having specific R11 groups possessing both ER α agonist /ER β antagonist activity, and the presently claimed compounds have been shown to possess ER α agonist /ER β antagonist activities which are not possessed by compound 5b of Lobaccaro et al. (see Tables A and B of the present specification), amended independent claims 1, 8 and 13 are nonobvious over Lobaccaro et al.

In view of the above, withdrawal of the rejection of claims 1, 7, 8, and 13 under 35 U.S.C. §103(a), is respectfully requested.

Claims 1, 2, 4, 7, 8, 13, 14 and 16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Napolitano et al., J. Med. Chem, Vol. 38, pp. 2774-2779, 1995 (Napolitano et al.). The Examiner essentially contends that since 1) Napolitano et al. teach that the compounds having 11 β -substituted estradiol derivatives having R11 with less than 5 carbon atoms are homologs of the claimed compounds; 2) the derivatives of Napolitano et al. show high affinity for estrogen receptor; 3) the estradiols of Napolitano are known estrogenic compounds and estradiol compounds are well known to be useful in methods for treating estrogen deficiency disorders, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the claimed compounds in a pharmaceutical composition and method for treating estrogen deficiency disorders.

As claims 2, 4, 14 and 16 have been cancelled without prejudice, and independent claims 1, 8 and 13 have been amended, Applicants address this §103 rejection with respect to the amended claims. Applicants traverse the rejection and respectfully submit that Napolitano et al. does not make obvious amended independent claims 1, 8 and 13.

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Napolitano et al. is directed to the synthesis of cyanoalkyl, ethynyl, propynyl and iodovinyl 11 β -substituted estradiol derivatives, i.e., derivatives having R11 with less than 5 carbon atoms, which are evaluated for binding affinity to the estrogen receptor and for their potential as imaging agents for estrogen receptor-positive breast tumors. Napolitano is merely concerned with designing high-affinity probes for the estrogen receptor for imaging and is not at all concerned with assessing the specific type of estrogenic activity, i.e., ER α agonist or ER β antagonist, possessed by the described derivatives. Indeed, it is duly noted that an imaging agent is used as a diagnostic tool and is typically not used for use in a pharmaceutical composition for treating estrogen deficiency disorders as is presently claimed. Further, Napolitano et al. is devoid of any teaching or specific suggestion that 11 β -estradiol derivatives having the specific R11 groups (having a total number of 5-6 carbon atoms) as recited in amended independent claims 1, 8 and 13 would possess both ER α -agonist activity and ER β -antagonist activity.

It is further noted that on page 10 of the outstanding Action, the Examiner refers to compound 3a/entry 5 as having a propynyl group, which is not correct because it is an ethynyl group, and compound 10/entry 11 as having an ethynyl group, which is not correct either because it is an ethenyl group. The structurally-closest compound 2a/entry 3, having 3 carbon atoms, can best be compared with compound 1 in Table B (having a terminal double bond instead of a triple bond) or with compound 9 (a propyl group instead of a 1-propynyl group). As can be seen from Table A, neither compound 1 nor compound 9 have the desired ER α agonist/ER β antagonist activity, whereas compound 5 having two carbon atoms more than compound 2a of Napolitano et al. possesses ER α agonist/ER β antagonist activity.

With respect to the binding affinity of the derivatives, Napolitano et al. further conclude that an 11 β -ethynyl group (i.e., compound 3a/entry 5 in Table 1) has a higher binding affinity to the estrogen receptor than an 11 β 1-propynyl group (i.e., compound 2a/entry 3). Accordingly, one skilled in the art armed with this teaching would not be motivated to modify the length of the chain to 5 carbon atoms as set forth in compound 5 of Table B.

Further, it can fairly be said that Napolitano et al. in actually teaching that the binding affinity markedly dropped when increasing the chain length from an ethynyl group to a propynyl group, specifically teaches away from the present invention in which the compound structurally most closest to the compounds of Napolitano et al., compound 5 in Table B, has five carbon atoms instead of 2 or 3.

In sum, since Napolitano et al. 1) teaches use of 11 β -substituted estradiol derivatives as a diagnostic tool and not as a pharmaceutical for treating estrogen deficiency disorders; 2) is completely silent that estradiol derivatives containing R11 groups as recited in amended claim 1

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possess ER α agonist/ER β antagonist activity; and 3) specifically teaches away from lengthening the R11 chain to 5 carbon atoms, one skilled in the art relying on Napolitano would not be motivated to increase the length of R11 to solve the problem of finding a compound that possessed both ER α agonist and ER β antagonist activities. In addition, the structurally closest compound to compound 2a/entry 3 (with 3 carbon atoms) of Napolitano, compounds 1 and 9 of Table A/Table B, do not possess ER α agonist/ER β antagonist activity, whereas compound 5 (with 5 carbon atoms) of Table A/Table B possesses ER α agonist and ER β antagonist activity. Accordingly, amended claims 1, 8 and 13 are nonobvious over Napolitano et al.

In view of the above, withdrawal of the rejection of claims 1, 7, 8, and 13 as unpatentable over Napolitano et al. is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below.

Respectfully submitted,



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